

**Evaluation of myocardial injury and quality of life of patients recovered from Coronavirus
Infectious Disease 19 (COVID-19)**

Approval Number 145 by Ethical Board as of 09/16/2020.

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The novel coronavirus disease 19 (COVID-19) pandemic made us to have a different look at the problem of cardiovascular injury by this virus. In the patients with severe course of COVID-19 there is approximately a 7% prevalence of fulminant myocarditis. Moreover, this infectious process worsens the outcomes of ischemic heart disease by accelerating the formation of intravascular thrombi (including intracoronary) and destabilizes the patients with chronic heart failure (Myocardial localization of coronavirus in COVID-19 cardiogenic shock. *Eur J Heart Fail* 2020; 22:911–915.; Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020; 395:1054–62; Cardiovascular Imaging in Evaluation of COVID-19 Complications. *J Am Coll Cardiol* 2020; 76:1345–57; Association of Cardiac Infection With SARS-CoV-2 in Confirmed COVID-19 Autopsy Cases. *JAMA Cardiol*. doi:10.1001/jamacardio.2020.3551).

The research conducted at the beginning of COVID-19 pandemic in China showed us that among patients with no known cardiovascular past medical history and persistent complaints of heart racing (palpitations) and chest pain after recovery there were pathological findings in 58% of participants confirmed by cardiac magnetic resonance (CMR). Furthermore, in 54% of cases there was swelling of myocardium and in 31% there were foci of fibrosis (Cardiac Involvement in Patients Recovered From COVID-2019 Identified Using Magnetic Resonance Imaging. *J Am Coll Cardiol Img* 2020. <https://doi.org/10.1016/j.jcmg.2020.05.004>).

Recent studies conducted in Germany and published in July 2020 demonstrated increase in the level of high-sensitivity troponin T (hsTropT) in 71% of patients following 2-3 months after recovery from COVID-19. Moreover, CMR imaging with contrast showed that in 78% of participants there were signs of myocardial tissue injury alongside with 60% of patients having signs of continuing myocardial inflammation (Outcomes of Cardiovascular Magnetic Resonance Imaging in Patients Recently Recovered From Coronavirus Disease 2019 (COVID-19). *JAMA Cardiol*. doi:10.1001/jamacardio.2020.3557).

International multipurpose study conducted in 7 hospitals of Milano and New-York demonstrated that 62.6% patients hospitalized with COVID – 19 had increased levels of cardiac troponins and 47,5% had structural heart abnormalities secondary to the infectious disease visualized on echocardiography (Characterization of Myocardial Injury via Patients With COVID-19. *J Am Coll Cardiol* 2020;76:2043–55).

According to these data patients after recovery from COVID-19 may have signs of injury not only of lung tissues but also the heart. This makes the correct and early diagnosis of such conditions, choice of optimal therapeutic strategy and rehabilitation procedures very important nowadays (Description and Proposed Management of the Acute COVID-19 Cardiovascular Syndrome. *Circulation*. 2020;141:1903–1914; Medical rehabilitation during novel coronavirus infectious disease - 19 (COVID-19). *Physical and rehabilitation medicine, medical rehabilitation*. 2020;2(2):140–189. DOI: <https://doi.org/10.36425/rehab34231>; Temporary methodical recommendations «Prophylaxis, diagnosis, and therapy of the novel coronavirus infection (COVID-19)», 9th edition, 10/26/2020).

The main goal of this observational non-interventional study is the evaluation of prevalence of myocardial injury (heart injury) of the participants recovered from the novel coronavirus infectious disease (COVID-19). Participants with signs of myocarditis (pericarditis) and/or myocardial fibrosis, and with a threat of heart failure development and other outcomes are selected into this study. In this cohort the percentage of participants having myocardial injury based on the level of high-sensitivity troponin, echocardiography (decreased Left Ventricle Ejection Fraction, abnormalities of wall motion, Right Ventricle dysfunction, increased

size of heart chambers above referential values, presence of pericardial effusion), cardiac MRI with contrast enhancement (presence of edema on T2-weighted images, presence of early and late gadolinium enhancement phenomenon, local motion abnormalities, increased size of heart chambers above referential values, presence of pericardial effusion). At 6 months of the dynamic follow-up, MRI with contrast enhancement will be repeated in the participants with established myocardial injury at inclusion to assess the percentage of the participants having ongoing myocardial injury (Comparative investigation of informative yield of non-invasive diagnostics methods of inflammatory diseases of myocardium. Russian cardiology journal 2018, 2 (154): 53–59; Cardiovascular Magnetic Resonance in Nonischemic Myocardial Inflammation. Expert Recommendations. Am Coll Cardiol 2018; 72: 3158–76.).

The secondary goal of the study is evaluation of quality of life of the patients recovered from the novel coronavirus infectious disease (COVID-19) by the means of EQ-5D and/or DASI questionnaire using the descriptive system of 5 components of quality of life related to the wellbeing, and visual analogue scale (Life quality of the Russian population by the data from ESSE-RF study. Cardiovascular Therapy and Prevention, 2016; 15(5): 84–90; Health-related quality of life population indicators using EQ–5D questionnaire. Health Care of the Russian Federation, Russian journal. 2018; 62(6): 295-303.).

All the received information during the study will be stored in a formalized form with the use of relational database developed based on Microsoft® Access. To be able to gain valid results of the study, quantitative variables will be presented as the mean arithmetical number with standard deviation and the median with the upper and lower quartiles. For nominal variables the absolute value of the sign and its proportion will be shown. Unrelated features will be compared using the Mann – Whitney test, and related ones using the Wilcoxon test. Comparison of quantitative variables will be conducted using Pearson's chi-squared test. Qualitative related variables will be analyzed using McNemar's test. To analyze the relationship between quantitative characteristics, regardless of the type of their distribution, as well as between ordinal variables, the Spearman rank correlation coefficients will be calculated. At the comparison of groups, the null hypothesis will be rejected if significance level is less than 0.05. In case of multiple comparisons, Bonferroni correction will be considered.

The study will be conducted under the circumstances of common clinical practice and with the use of diagnostic methods and treatment approaches according to the current clinical guidelines of professional societies and clinical recommendations (Schultz J.C. et al. Diagnosis and Treatment of Viral Myocarditis // Mayo Clin. 2736 Proc. 2009. Vol. 84, № 11. P. 1001–1009.; International Consensus Group on Cardiovascular Magnetic Resonance in Myocarditis. Cardiovascular magnetic resonance in myocarditis: A JACC White Paper. J Am Coll Cardiol. 2009; 53: 1475–1487.; Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis. European Heart Journal July 3, 2013.; 2016 ESC Guidelines For The Diagnosis And Treatment Of Acute And Chronic Heart Failure. European Heart Journal (2016), 37: 2129–2200; 16. Guidelines for the management of myocarditis. Eurasian cardiology journal 2015; 3:5–17; Clinical recommendations on myocarditis of the Healthcare Ministry of the Russian federation, http://www.consultant.ru/document/cons_doc_LAW_326148/8efd5f17af55cb35a770f73937590c642437b7eb/).

Main inclusion criteria into the study are:

- i. Adult patients of age above 18 years with diagnosed SARS-CoV-2 infection based on the PCR (polymerase chain reaction) and/or quantitative tests of IgM and IgG antibodies in serum;
- ii. Pneumonia development confirmed by chest computed tomography;

- iii. Negative PCR test for SARS-CoV-2 at the time of inclusion into the study;
- iv. Stable patient state allowing outpatient follow-up;
- v. Signed informed consent.

Main exclusion criteria are:

- i. Absence of convincing data confirming SARS-CoV-2 infection of a participant at the time of inclusion;
- ii. Absence of medical records regarding previous treatment of COVID-19;
- iii. Low compliance and unwillingness to undergo defined examinations;
- iv. Absence of informed consent.

In this observational study the general examination of all patients who meet the inclusion criteria will be performed. Following dynamic observation and follow-up will be conducted only for those patients in whom presence of myocardial injury is established according to the echocardiography and/or cardiac MRI with contrast enhancement. Follow-up visits are scheduled at 3, 6, 9, and 12 months from the time of inclusion with an acceptable variation of a visit date up to 4 weeks.

During the general medical check-up and following follow-up visits the participants' complaints, vital signs, physical examination, quality of life (EQ-5D and DASI questionnaire) are being assessed.

Common laboratory tests, cardio-specific enzymes, ECG, echocardiography, 24-hour Holter ECG may also be performed in case of complaints of cardiac rhythm abnormalities. All patients will undergo the cardiac MRI with contrast enhancement at the inclusion to the study. Patients with established myocardial injury will undergo the second cardiac MRI with contrast enhancement 6 months later. Based on the results, the multi-spiral CT of the thoracic internal organs, pulmonologist consultation, and/or other examinations may be performed.

In the process of observation, development of these clinical events in the participants will be recorded based on the comprehensive medical records and other sources of information:

- i. Myocardial infarction – any type of impairment of coronary blood flow with a typical clinical presentation, ECG changes, increase of specific cardiac enzymes;
- ii. Atypical angina followed by hospitalization;
- iii. Acute brain perfusion impairment – any type of developed acute impairment of brain blood flow;
- iv. Pulmonary artery thromboembolism;
- v. Decompensation of a known heart failure;
- vi. Atrial fibrillation or quivering of atria – confirmation by ECG and/or 24-hour ECG monitoring of paroxysms longer than 30 seconds in duration;
- vii. Bleeding of any localization followed by seeking of medical care.

Should a lethal outcome take place, the whole medical information will be requested including medical death certificates. Lethal outcomes will be divided into these categories:

- i. Sudden death – unexpected death of a stable participant within a few hours since first signs of a distress;
- ii. Cardiovascular death – the death associated with the development of previously diagnosed cardiovascular disease in a participant (acute myocardial infarction, stroke, massive pulmonary thromboembolism etc.);
- iii. Non-cardiovascular death – the death which is not linked to any of the categories mentioned above and is associated with other pathological processes (cancer, bleeding, trauma etc.).

Summary of the study is shown below.

Summary of the study

Data collection	Inclusion into the study ¹	Follow-up visit at 3 months (±4weeks) ²	Follow-up visit at 6 months (±4weeks)	Follow-up visit at 9 months (±4weeks)	Follow-up visit at 12 months (±4weeks)
Past medical history, including evaluation of the diseases preceding the COVID-19	+				
Features of the COVID-19 course and treatment	+				
Complaints, physical examination	+	+	+	+	+
Laboratory tests	+	+ ³	+		+
ECG	+		+		+
Echocardiography	+				+
24-hour ECG monitoring ⁴	+		+		+
Multi-spiral CT of the thoracic internal organs ⁵	+		+		
Cardiac MRI with contrast enhancement	+		+		
Evaluation of physical state and functional class, physical activity, level of shortness of breath	+	+	+	+	+
Evaluation of quality of life with EQ-5D and/or DASI questionnaire	+	+	+		+
Treatment and treatment correction	+	+	+	+	+
Clinical outcomes evaluation	+	+	+	+	+

¹ Performed in all patients included into the study.

² Following observation and examinations are performed only in patients with established myocardial (heart) injury at the inclusion.

³ Repeated laboratory tests are performed only in patients with revealed abnormalities at the inclusion into the study.

⁴ Only in patients with established heart rhythm abnormalities at the inclusion.

⁵ Based on the pulmonologist's opinion for evaluation of residual changes.

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